P&S Heterogeneous Systems

Algorithmic Improvement and GPU Acceleration of the GenASM Algorithm

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Genome Sequencing & Analysis

Genome Sequencing

- **Genome sequencing:** Enables us to determine the order of the DNA sequence in an organism's genome
  - Plays a pivotal role in:
    - Personalized medicine
    - Outbreak tracing
    - Understanding of evolution

Genome

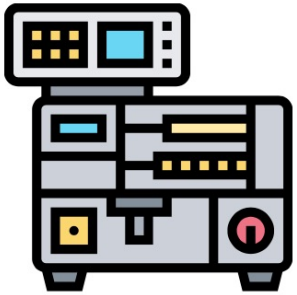
DNA

- **Challenges:**
  - There is no sequencing machine that takes long DNA as an input, and gives the complete sequence as output
  - Sequencing machines extract small randomized fragments of the original DNA sequence

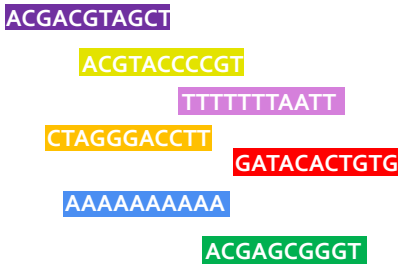
Genome Sequencing (cont'd)

Sample Collection

Chopped DNA fragments



Sequencing



Sequenced reads

Large DNA molecule

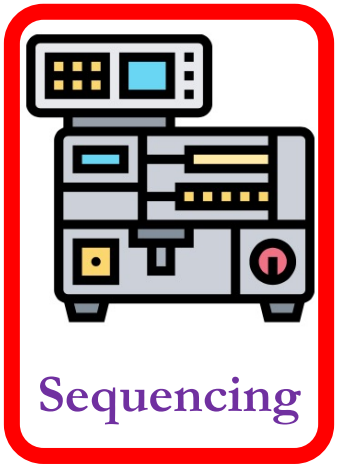
Preparation

Genome Sequence Analysis

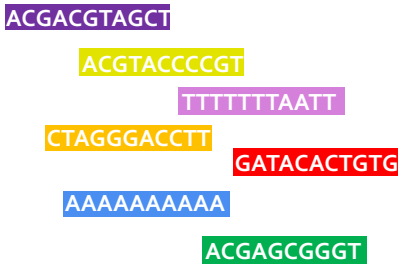
Genome Sequencing (cont'd)

Sample Collection

Chopped DNA fragments



Sequencing



Sequenced reads

Large DNA molecule

Preparation

Genome Sequence Analysis

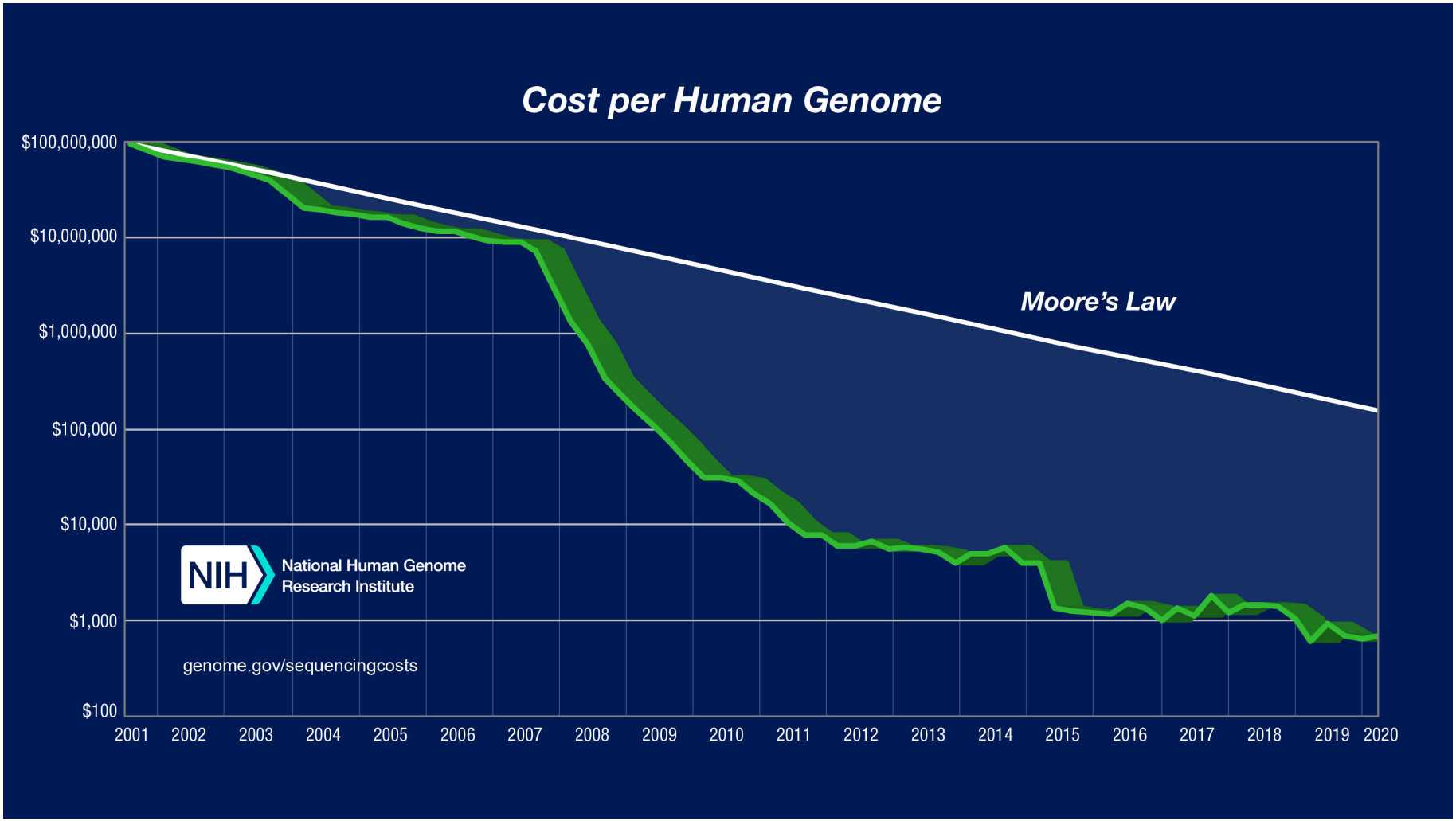
Sequencing Technologies

Oxford Nanopore (ONT)

PacBio

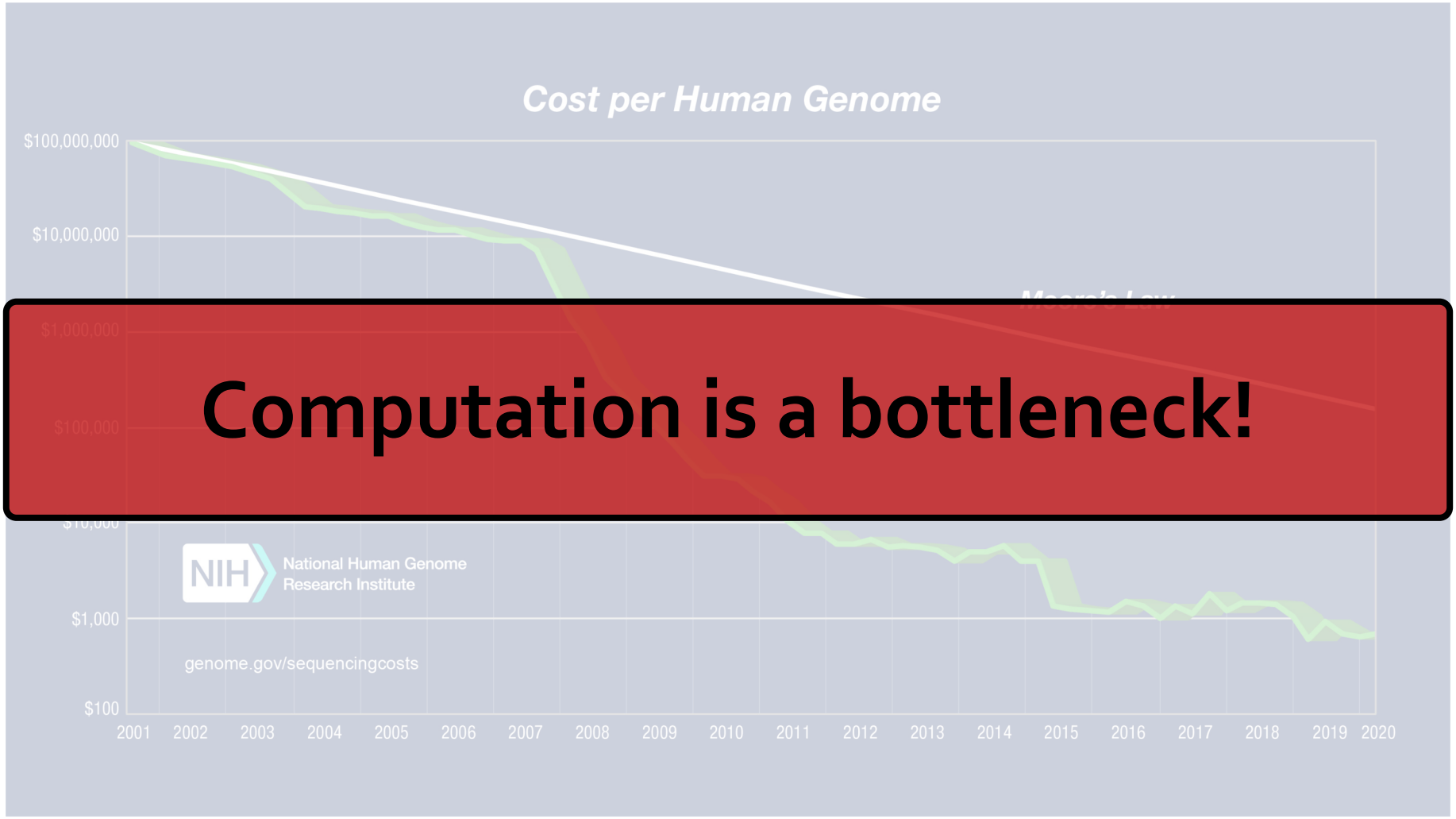
Illumina

Current State of Sequencing



*From NIH (https://www.genome.gov/about-genomics/fact-sheets/DNA-Sequencing-Costs-Data)

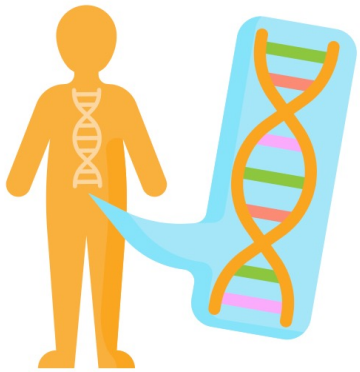
Current State of Sequencing



Computation is a bottleneck!

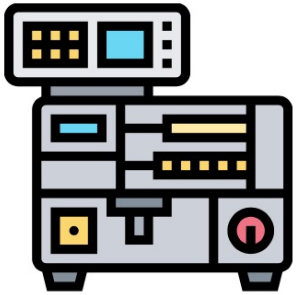
*From NIH (https://www.genome.gov/about-genomics/fact-sheets/DNA-Sequencing-Costs-Data)

Genome Sequencing (cont'd)

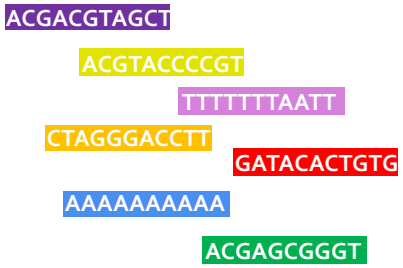


Sample Collection

Chopped DNA fragments



Sequencing



Sequenced reads

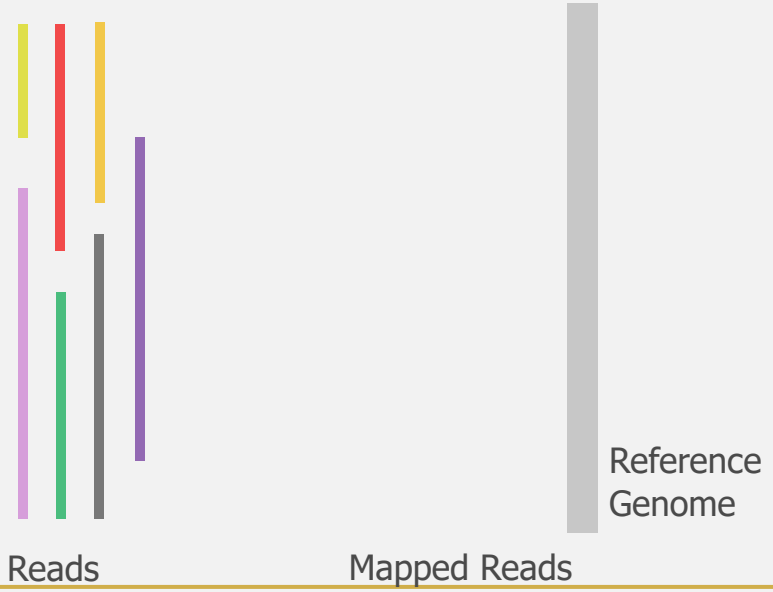
Preparation

Large DNA molecule

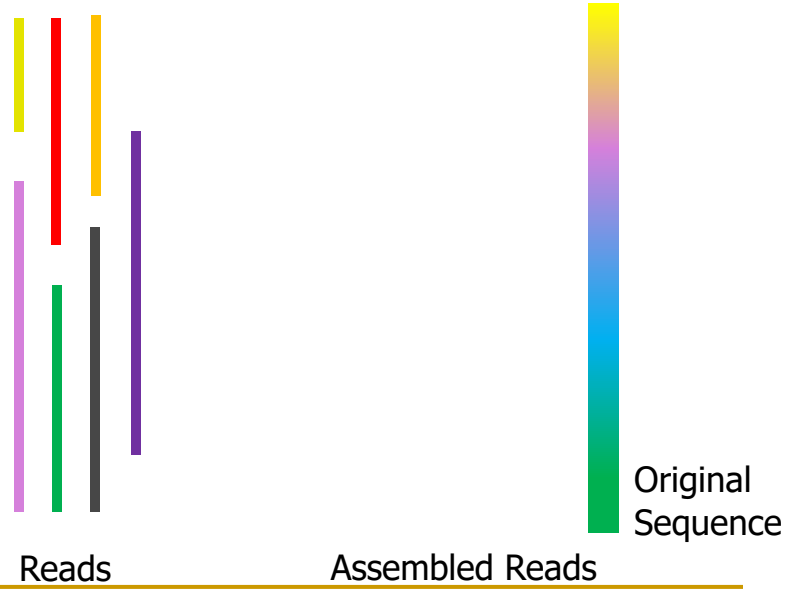
Genome Sequence Analysis

Genome Sequence Analysis

Read Mapping, method of aligning the reads against the reference genome in order to **detect matches and variations.**



***De novo* Assembly,** method of merging the reads in order to **construct** the original sequence.



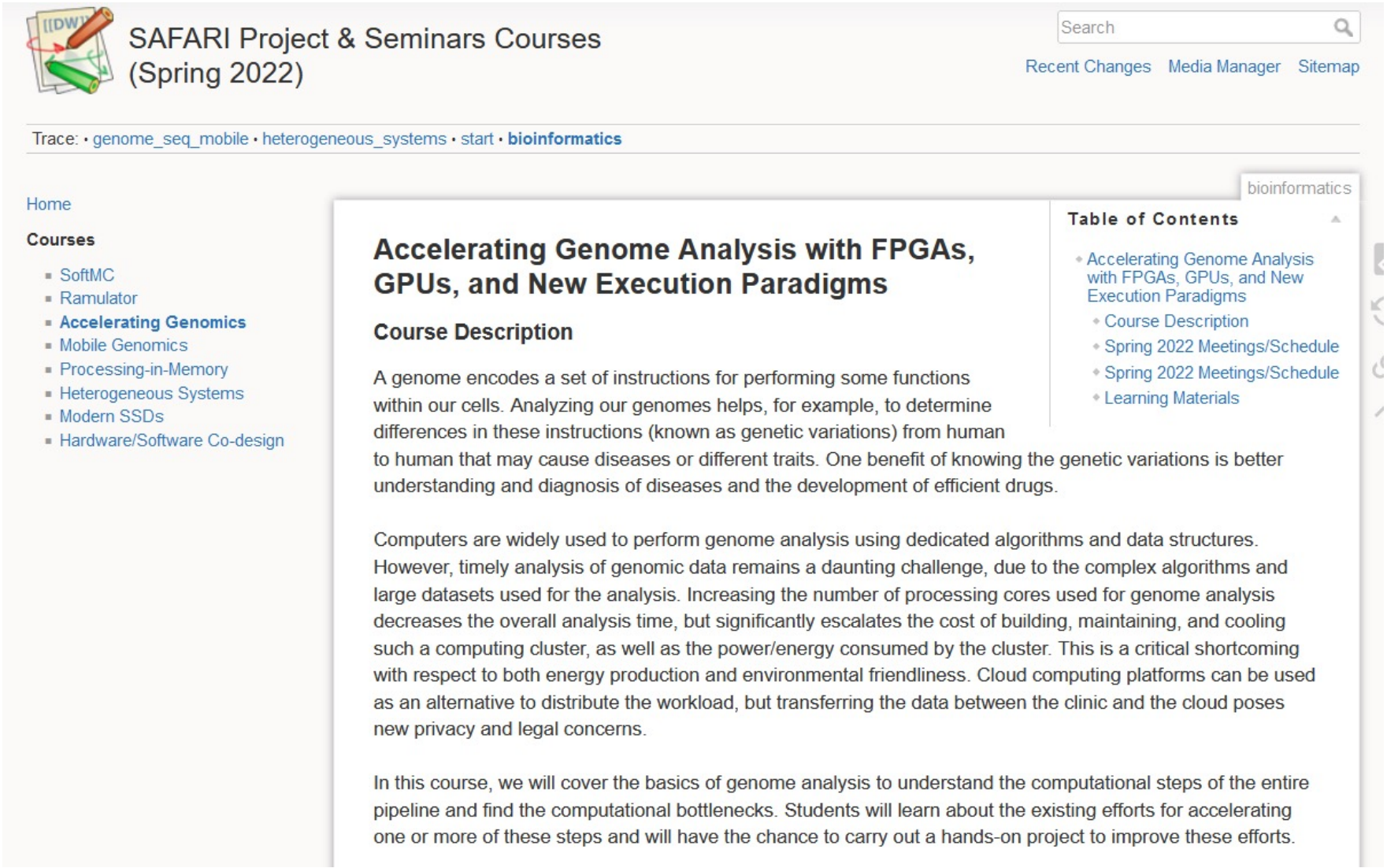
GSA with Read Mapping

- **Read mapping:** *First key step* in genome sequence analysis (GSA)
  - Aligns reads to one or more possible locations within the reference genome, and
  - Finds the matches and differences between the read and the reference genome segment at that location

- Multiple steps of read mapping require ***approximate string matching***
  - Approximate string matching (ASM) enables read mapping to account for sequencing errors and genetic variations in the reads

- Bottlenecked by the computational power and memory bandwidth limitations of existing systems

More on Genomics



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bioinformatics

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  - Spring 2022 Meetings/Schedule
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Accelerating Genome Analysis with FPGAs, GPUs, and New Execution Paradigms

Course Description

A genome encodes a set of instructions for performing some functions within our cells. Analyzing our genomes helps, for example, to determine differences in these instructions (known as genetic variations) from human to human that may cause diseases or different traits. One benefit of knowing the genetic variations is better understanding and diagnosis of diseases and the development of efficient drugs.

Computers are widely used to perform genome analysis using dedicated algorithms and data structures. However, timely analysis of genomic data remains a daunting challenge, due to the complex algorithms and large datasets used for the analysis. Increasing the number of processing cores used for genome analysis decreases the overall analysis time, but significantly escalates the cost of building, maintaining, and cooling such a computing cluster, as well as the power/energy consumed by the cluster. This is a critical shortcoming with respect to both energy production and environmental friendliness. Cloud computing platforms can be used as an alternative to distribute the workload, but transferring the data between the clinic and the cloud poses new privacy and legal concerns.

In this course, we will cover the basics of genome analysis to understand the computational steps of the entire pipeline and find the computational bottlenecks. Students will learn about the existing efforts for accelerating one or more of these steps and will have the chance to carry out a hands-on project to improve these efforts.

https://safari.ethz.ch/projects_and_seminars/spring2022/doku.php?id=bioinformatics

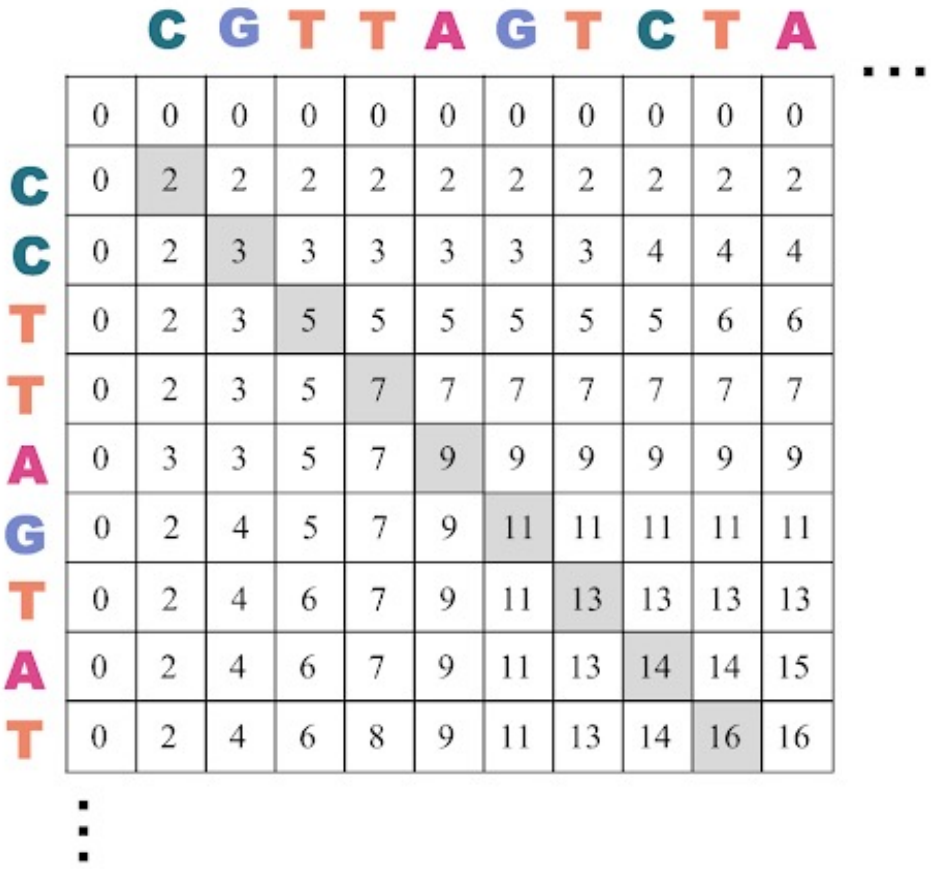
Approximate String Matching

Approximate String Matching

- Sequenced genome may not exactly map to the reference genome due to genetic variations and sequencing errors

- **Approximate string matching (ASM):**
  - Detect the differences and similarities between two sequences
  - In genomics, ASM is required to:
    - Find the *minimum edit distance* (i.e., total number of differences)
    - Find the *optimal alignment* with a *traceback* step
      - Sequence of matches, substitutions, insertions and deletions, along with their positions
  - Usually implemented as a dynamic programming (DP) based algorithm

Arithmetic Dynamic Programming for Approximate String Matching



		C	G	T	T	A	G	T	C	T	A	…
	0	0	0	0	0	0	0	0	0	0	0	
C	0	2	2	2	2	2	2	2	2	2	2	
C	0	2	3	3	3	3	3	3	4	4	4	
T	0	2	3	5	5	5	5	5	5	6	6	
T	0	2	3	5	7	7	7	7	7	7	7	
A	0	3	3	5	7	9	9	9	9	9	9	
G	0	2	4	5	7	9	11	11	11	11	11	
T	0	2	4	6	7	9	11	13	13	13	13	
A	0	2	4	6	7	9	11	13	14	14	15	
T	0	2	4	6	8	9	11	13	14	16	16	
⋮												

Commonly-used algorithm for ASM in genomics…

…with quadratic time and space complexity

Bitvector-Based Dynamic Programming for Approximate String Matching: Bitap Algorithm

Text	A	C	G	T	-
Exact Match	1111	1111	1111	1111	1111
1 Edit	0110	1010	1100	1110	1110
2 Edits	0000	0000	1000	1100	1100
3 Edits	0000	0000	0000	1000	1000
4 Edits	0000	0000	0000	0000	0000

- **Two-dimensional**, but different axes
- Entries are **bitvectors** instead of numbers

Bitap Algorithm

```
For each character of the text (char):                    Outer Loop
    Copy previous R bitvectors as oldR                    Bitwise Operations
    R[0] = (oldR[0] << 1) | PM [char]
    For d = 1…k:                                          Inner Loop
        deletion      = oldR[d-1]                         Bitwise Operations
        substitution  = oldR[d-1] << 1
        insertion     =    R[d-1] << 1
        match         =(oldR[d  ] << 1) | PM [char]
        R[d] = deletion & mismatch & insertion & match
Check MSB of R[d]:                                        Output
    If 1, no match.
    If 0, match with d many errors.
```

Traceback is Required

2. However, we also require the **optimal sequence of edits** ("CIGAR string")

		C	G	T	T	A	G	T	C	T	A
	0	0	0	0	0	0	0	0	0	0	0
C	0	2	2	2	2	2	2	2	2	2	2
C	0	2	3	3	3	3	3	3	4	4	4
T	0	2	3	5	5	5	5	5	5	6	6
T	0	2	3	5	7	7	7	7	7	7	7
A	0	3	3	5	7	9	9	9	9	9	9
G	0	2	4	5	7	9	11	11	11	11	11
T	0	2	4	6	7	9	11	13	13	13	13
A	0	2	4	6	7	9	11	13	14	14	15
T	0	2	4	6	8	9	11	13	14	16	16

1. So far we only have the **optimal score**

The CIGAR string is obtained through "**traceback**", i.e., following the optimal solution through the table

GenASM

- Damla Senol Cali, Gurpreet S. Kalsi, Zulal Bingol, Can Firtina, Lavanya Subramanian, Jeremie S. Kim, Rachata Ausavarungnirun, Mohammed Alser, Juan Gomez-Luna, Amirali Boroumand, Anant Nori, Allison Scibisz, Sreenivas Subramoney, Can Alkan, Saugata Ghose, and Onur Mutlu, **"GenASM: A High-Performance, Low-Power Approximate String Matching Acceleration Framework for Genome Sequence Analysis"**
  *Proceedings of the 53rd International Symposium on Microarchitecture (**MICRO**)*, Virtual, October 2020.
  [Lighting Talk Video (1.5 minutes)]
  [Lightning Talk Slides (pptx) (pdf)]
  [Talk Video (18 minutes)]
  [Slides (pptx) (pdf)]

GenASM: A High-Performance, Low-Power Approximate String Matching Acceleration Framework for Genome Sequence Analysis

Damla Senol Cali[†⋈] Gurpreet S. Kalsi[⋈] Zülal Bingöl[▽] Can Firtina[◇] Lavanya Subramanian[‡] Jeremie S. Kim[◇†]
Rachata Ausavarungnirun[⊙] Mohammed Alser[◇] Juan Gomez-Luna[◇] Amirali Boroumand[†] Anant Nori[⋈]
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[‡]*Facebook* [⊙]*King Mongkut's University of Technology North Bangkok* [⋆]*University of Illinois at Urbana–Champaign*

GenASM Extends Bitap

- Adds traceback
- Performance improvements
  - Windowing heuristic
  - Intra-task parallelism

GenASM's Traceback

```
For each character of the text (char):
    Copy previous R bitvectors as oldR
    R[0] = (oldR[0] << 1) | PM [char]
    For d = 1…k:
        deletion     = oldR[d-1]
        substitution = oldR[d-1] << 1
        insertion    =    R[d-1] << 1
        match        =(oldR[d  ] << 1) | PM [char]
        R[d] = deletion & mismatch & insertion & match
Check MSB of R[d]:
    If 1, no match.
    If 0, match with d many errors.
```

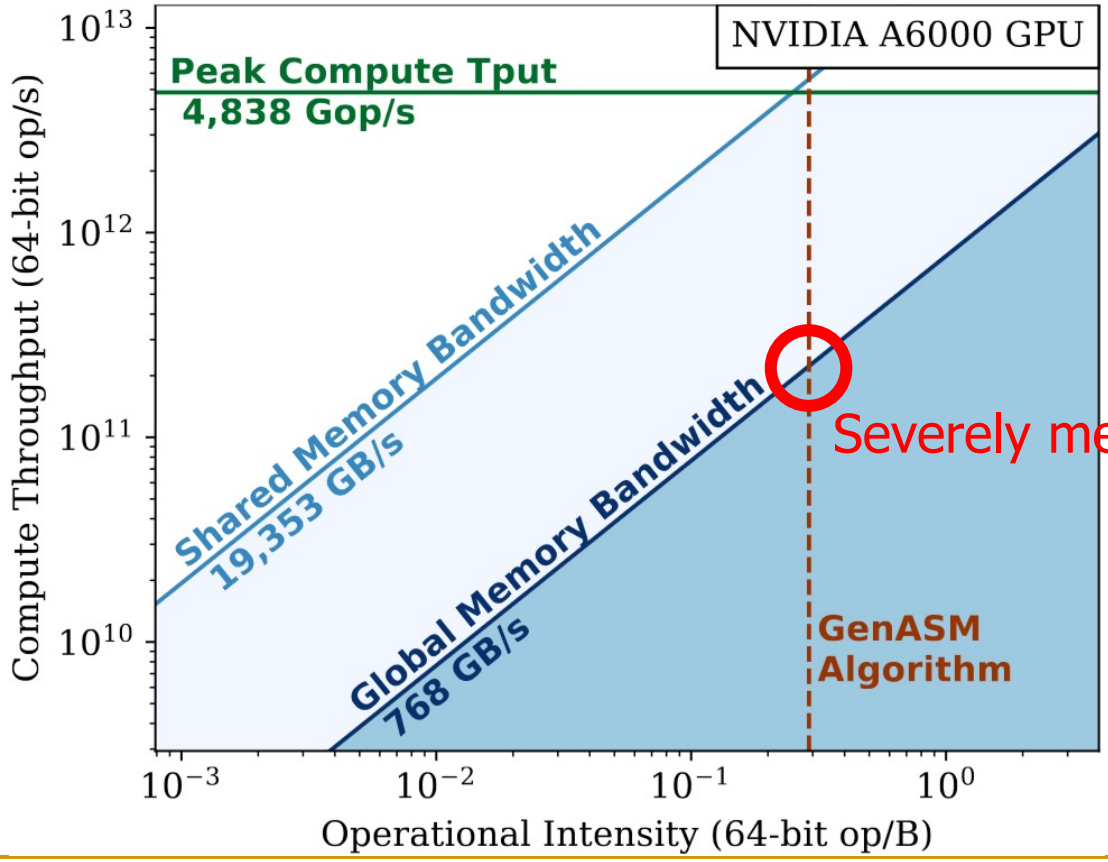
1. Store these

2. Follow a trail of 0's in the stored bitvectors

Accelerating GenASM on GPUs

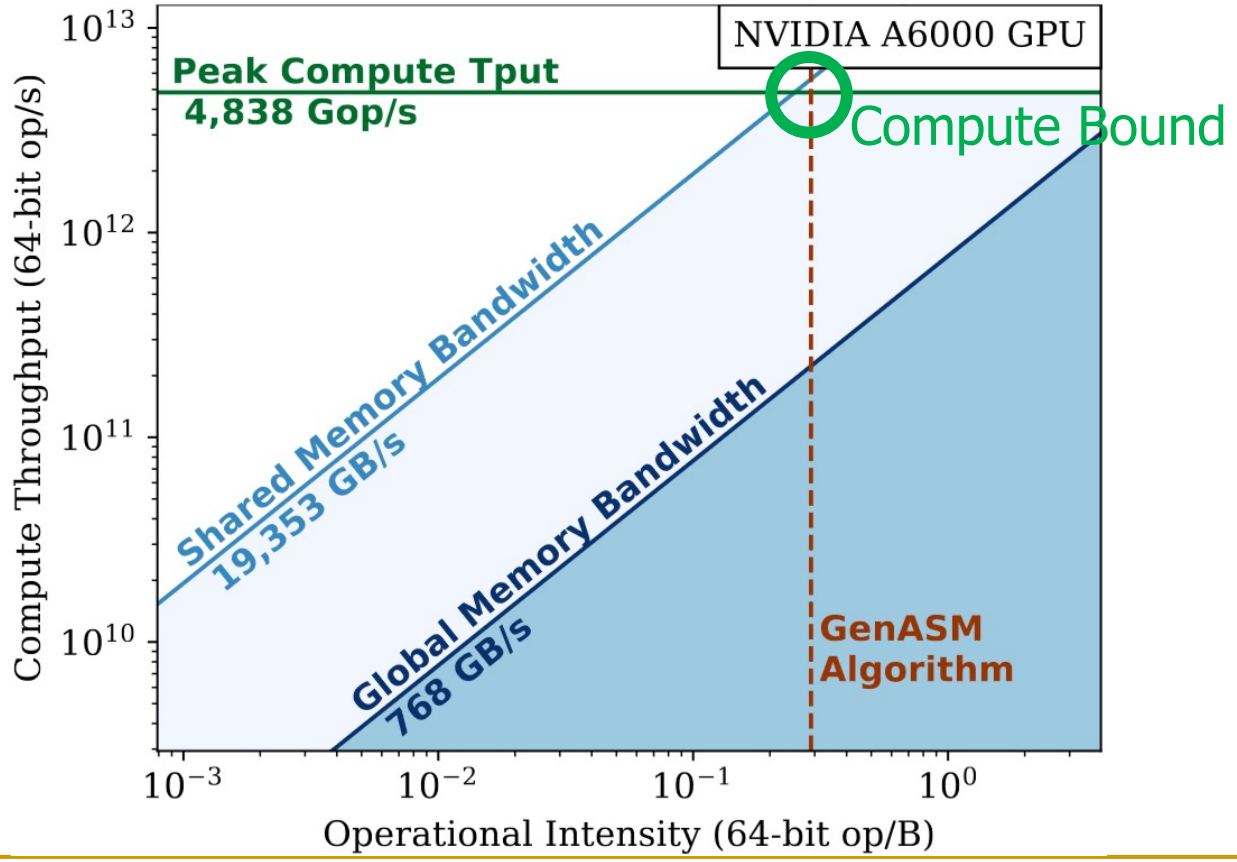
Implementation Attempt #1

- Compile existing C code with CUDA, with minor changes
- One **GPU thread** per sequence **pair**
- Store the DP table in **global memory**



Implementation Attempt #2

- Compile existing C code with CUDA, with minor changes
- One **GPU thread** per sequence **pair**
- Store the DP table in **shared memory** **has limited capacity**



Recall: GenASM's Traceback

```
For each character of the text (char):
    Copy previous R bitvectors as oldR
    R[0] = (oldR[0] << 1) | PM [char]
    For d = 1…k:
        deletion     = oldR[d-1]
        substitution = oldR[d-1] << 1
        insertion    =    R[d-1] << 1
        match        =(oldR[d  ] << 1) | PM [char]
        R[d] = deletion & mismatch & insertion & match
Check MSB of R[d]:
    If 1, no match.
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```
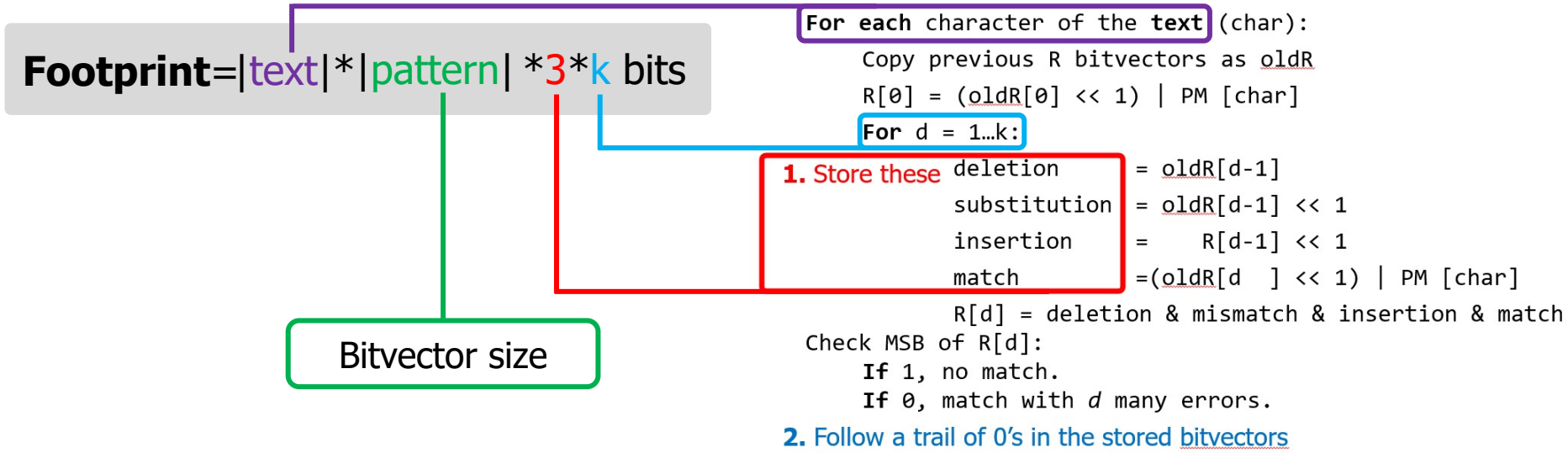

1. Store these

2. Follow a trail of 0's in the stored bitvectors

GenASM's Memory Footprint



Memory Footprint of Implementation Attempt #2

Assume

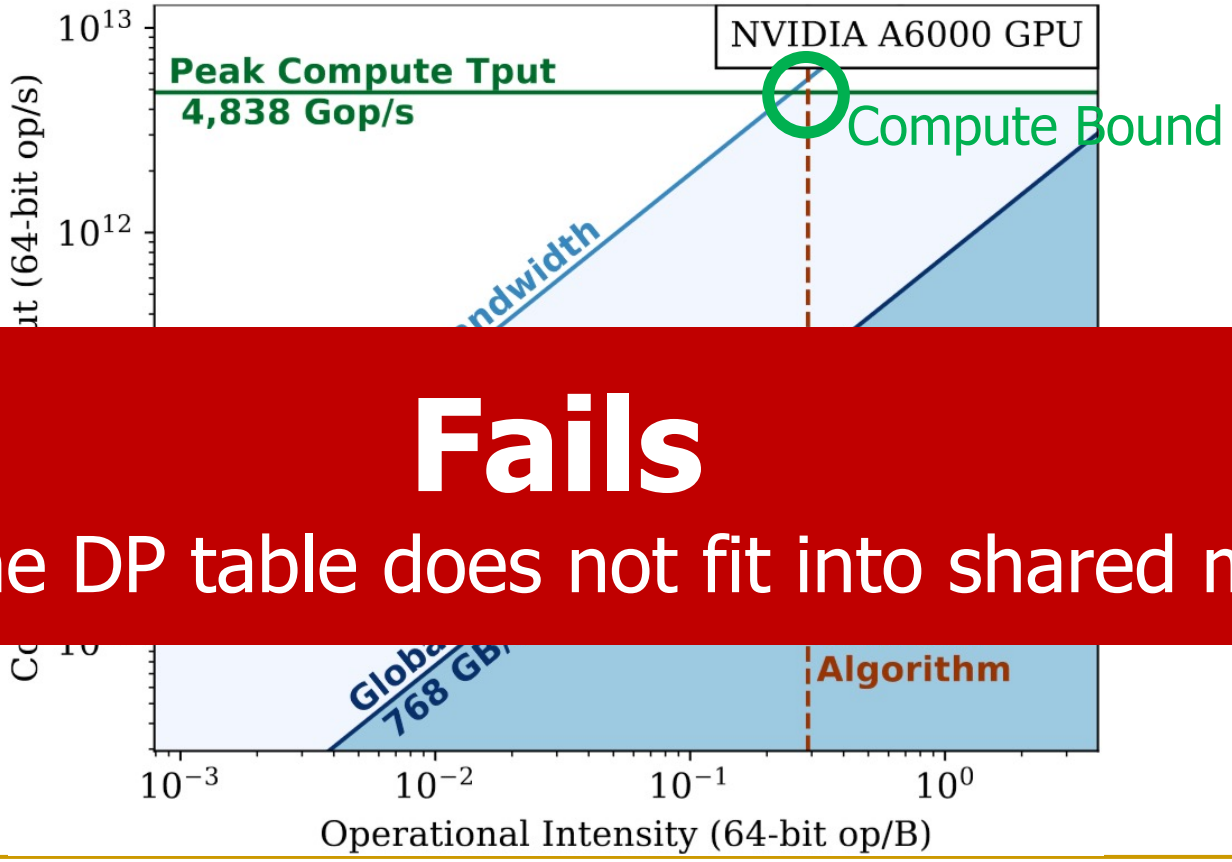
- |text|=|pattern|=k=64
- One warp of 32 threads

Footprint =64*64*3*64 bits * 32
=96KiB * 32
=3MiB

Shared memory capacity of he NVIDIA A6000 GPU: **99KiB** per SM

Implementation Attempt #2

- Compile existing C code with CUDA, with minor changes
- One **GPU thread** per sequence **pair**
- Store the DP table in **shared memory** **has limited capacity**

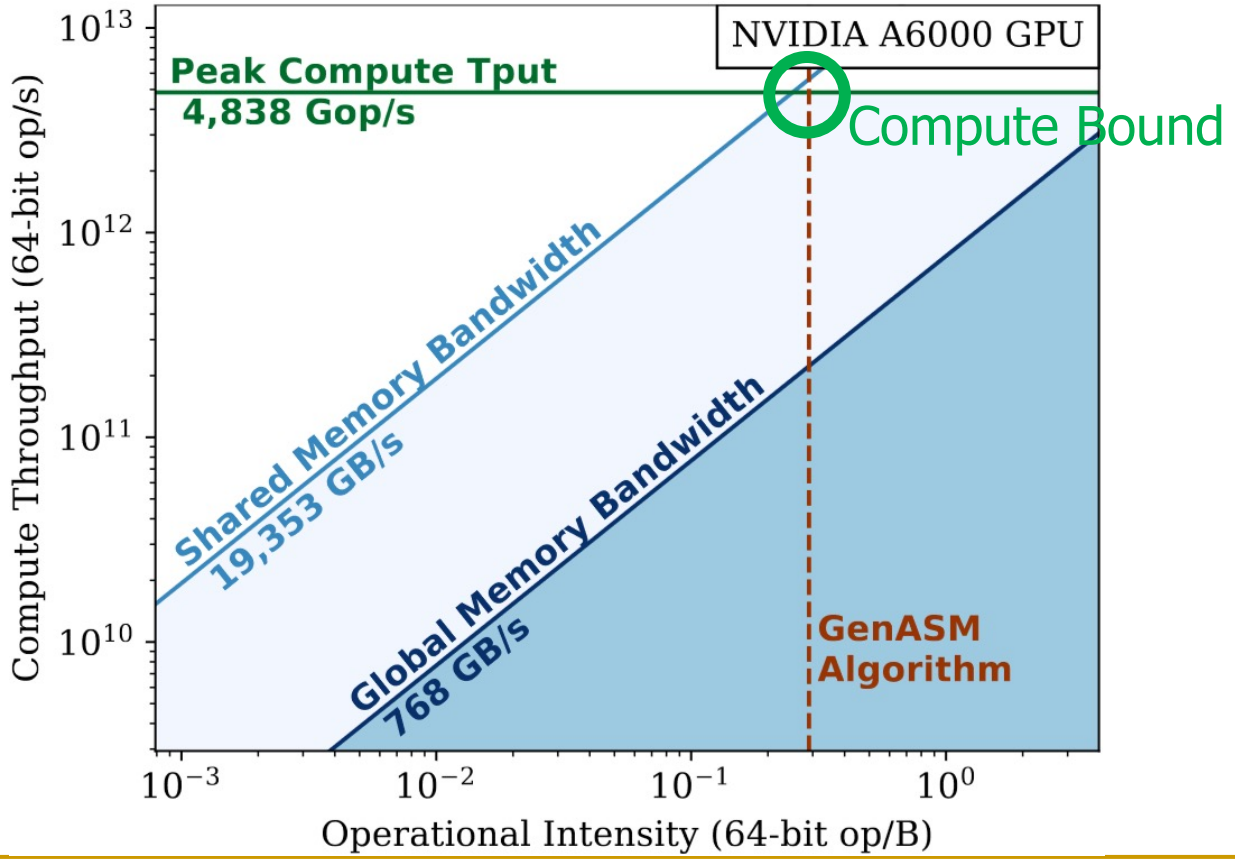


Fails

Because the DP table does not fit into shared memory

Implementation Attempt #3

- Rewrite code for GPUs
- **64 threads** in a thread block **cooperate** per seq. pair
- Store the DP table in **shared memory**



Mapping Threads to DP Cells

Text	A	C	G	T	-
Exact Match	1111	1111	1111	1111	1111
1 Edit	0110	1010	1100	1110	1110
2 Edits	0000	0000	1000	1100	1100
3 Edits	0000	0000	0000	1000	1000
4 Edits	0000	0000	0000	0000	0000
	Thread 0	Thread 1	Thread 2	Thread 3	

Memory Footprint of Implementation Attempt #3

Assume

- |text|=|pattern|=k=64
- 1 thread block

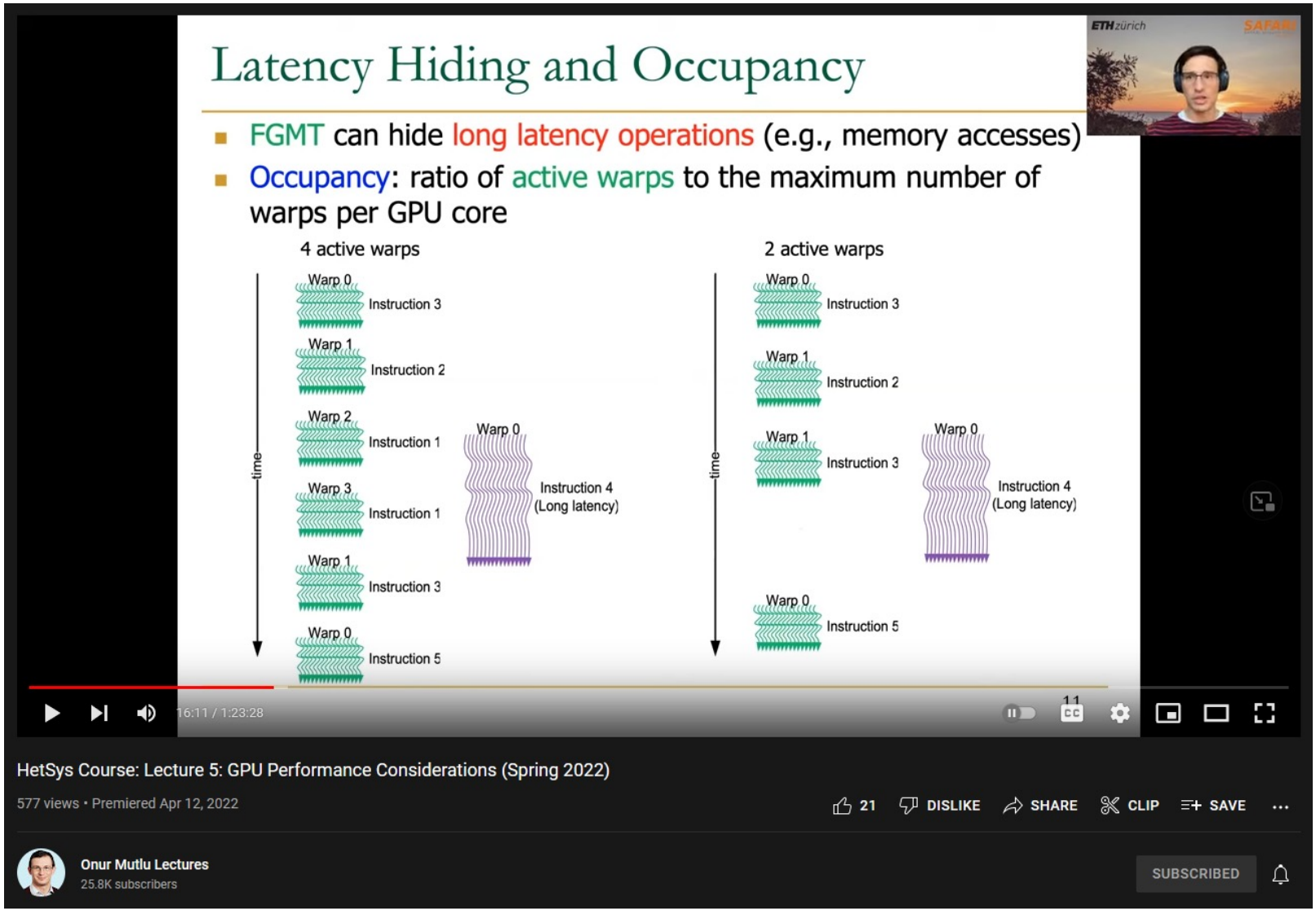
Footprint =64*64*3*64 bits * 1
=96KiB * 1
=96KiB

Shared memory capacity of he NVIDIA A6000 GPU: **99KiB** per SM

Occupancy Problem of Implementation Attempt #3

- Due to the memory footprint and shared memory capacity, at most **1 thread block** of **64 threads** can be **active** per SM
- This is called **"low occupancy"**
- Occupancy **should be high** for good performance
  - **Simultaneous multithreading** **hides** instruction **latencies**, but requires **multiple active warps** to work

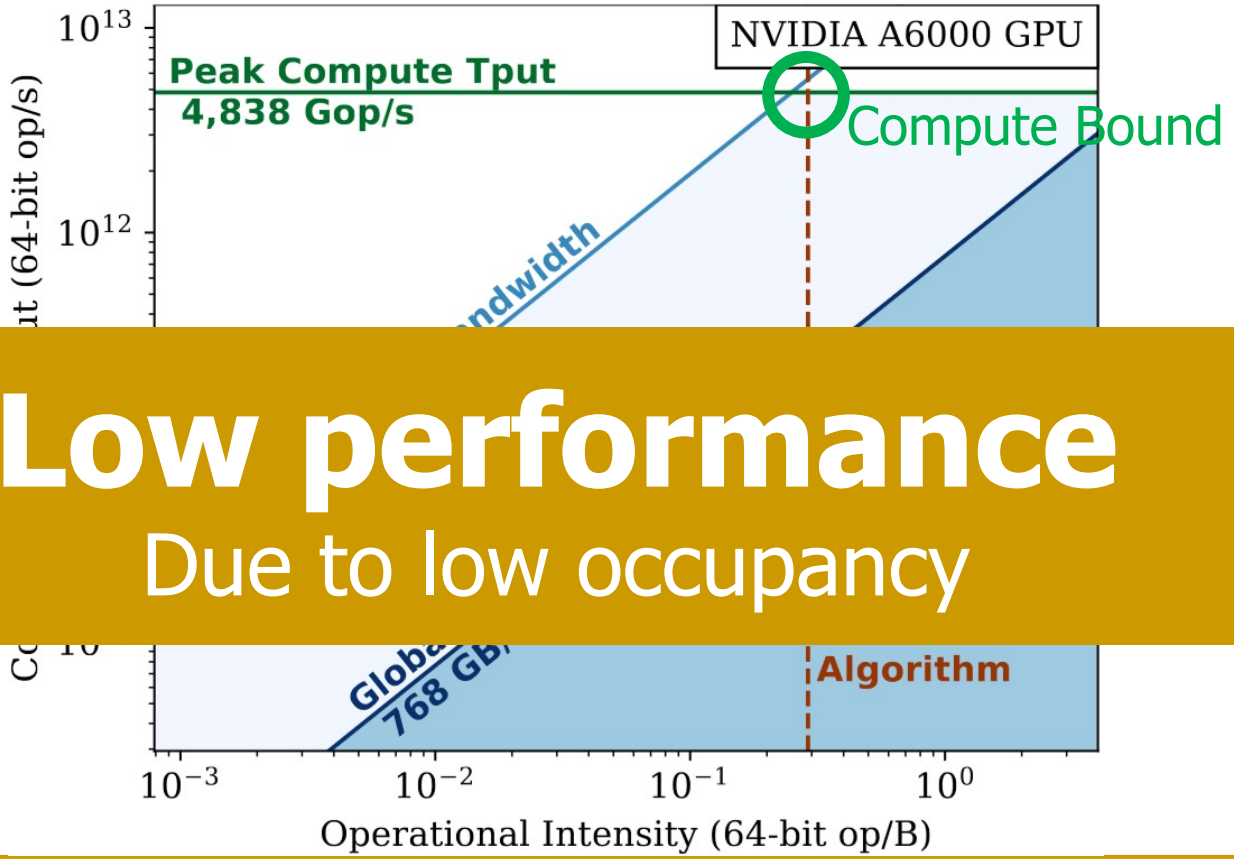
More About Occupancy



https://youtu.be/BYkPHLaFATM

Implementation Attempt #3

- Rewrite code for GPUs
- **64 threads** in a thread block **cooperate** per seq. pair
- Store the DP table in **shared memory**



Low performance

Due to low occupancy

Scrooge

- Joël Lindegger, Damla Senol Cali, Mohammed Alser, Juan Gomez-Luna, and Onur Mutlu, **"Algorithmic Improvement and GPU Acceleration of the GenASM Algorithm"** *Proceedings of the 21st IEEE International Workshop on High Performance Computational Biology (**HiCOMB**)*, Virtual, May 2022.
  [Slides (pptx) (pdf)]

Algorithmic Improvement and GPU Acceleration of the GenASM Algorithm

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Scrooge – Executive Summary

Motivation

- **Pairwise sequence alignment** is a **bottleneck** in genomic pipelines (e.g., read mapping)
- **GenASM** is a **state-of-the-art** sequence aligner, its hardware implementation is up to **10,000x faster** than prior software aligners and draws **500x less power**

Problem

Three inefficiencies in the GenASM algorithm limit its throughput and energy efficiency:

1. It has a **large memory footprint**
2. It has a **high bandwidth pressure**
3. It does some **unnecessary work**

Goal

Enable **fast** and **efficient** implementations of GenASM for CPUs, GPUs, and ASICs

Scrooge

Three novel algorithmic improvements to the **GenASM algorithm**:

- ***SENE*** and ***DENT*** reduce the **memory footprint** and **data movement** of GenASM
- ***Early Termination*** eliminates **unnecessary work**

High-performance **CPU** and **GPU implementations**

Results

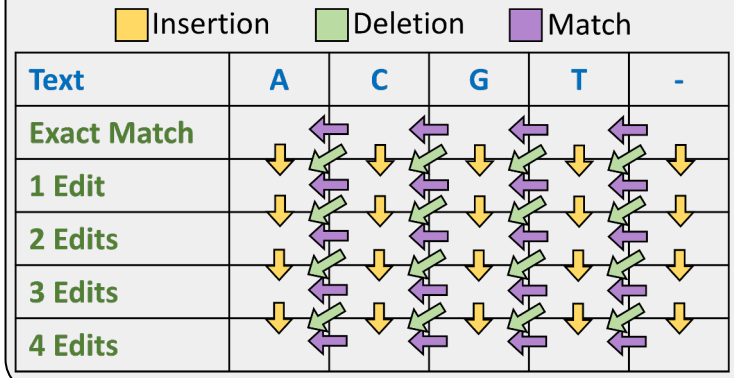
- **12-24x memory footprint reduction**
- **1.9x speedup** over GenASM on a recent CPU (Xeon Gold 5118)
- **5.9x speedup** over GenASM on a recent GPU (NVIDIA A6000)
- Similar improvements to be expected for ASICs

Lindegger+, "Algorithmic Improvement and GPU Acceleration of the GenASM Algorithm", HiCOMB 2022

Algorithmic Improvement 1: Store Entries, Not Edges (SENE)

GenASM

Stores **3 edges** per table entry **for traceback**



SENE Improvement

Scrooge

Stores table **entries** directly, edges are **regenerated**

Table Entry 1111

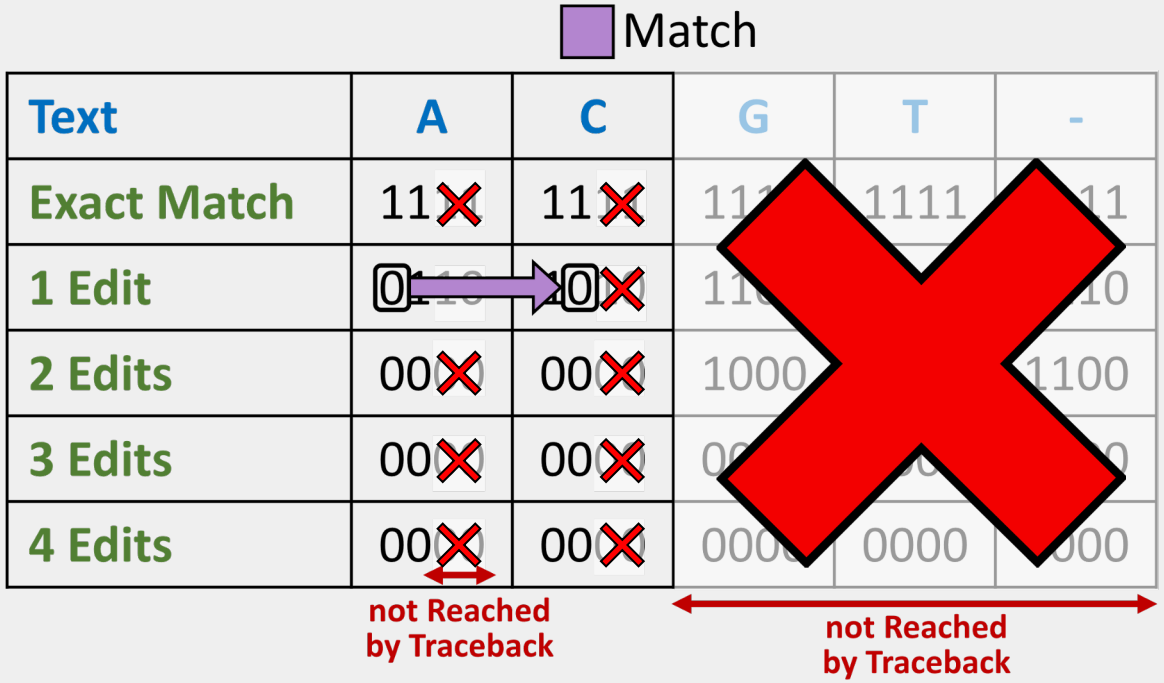
Text	A	C	G	T	-
Exact Match	1111	1111	1111	1111	1111
1 Edit	0110	1010	1100	1110	1110
2 Edits	0000	0000	1000	1100	1100
3 Edits	0000	0000	0000	1000	1000
4 Edits	0000	0000	0000	0000	0000

SENE results in a **3x reduction** in **memory footprint** and **data movement**

Algorithmic Improvement 2: Discard Entries Not used by Traceback (DENT)

GenASM's **traceback** does **not cross** the **entire table**

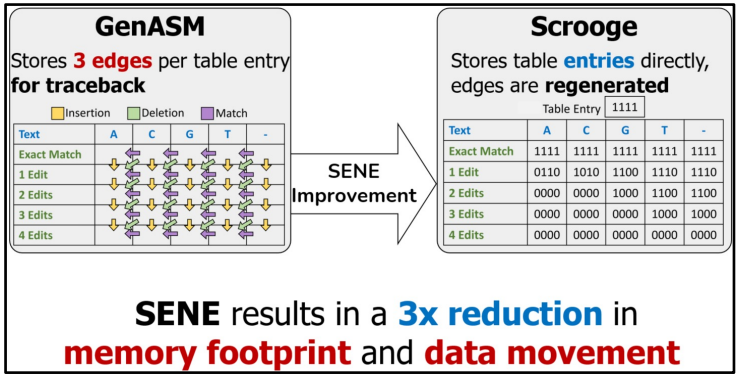
Scrooge discards entries that are **never reached**

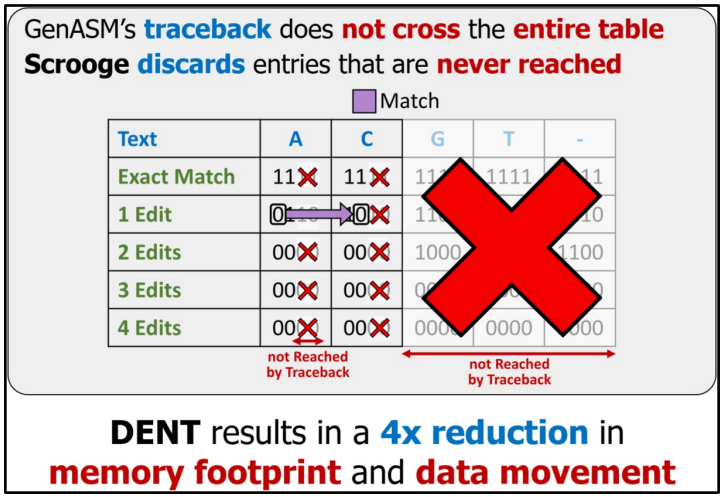


DENT results in a **4x reduction** in **memory footprint** and **data movement**

Implementation Attempt #4 – Scrooge

- **64 threads** in a thread block **cooperate** per seq. pair
- Store the DP table in **shared memory**
- **Algorithmically reduced memory footprint**





SENE+DENT results in a **12x reduction** in **memory footprint** and **data movement**

Scrooge's Memory Footprint

Assume

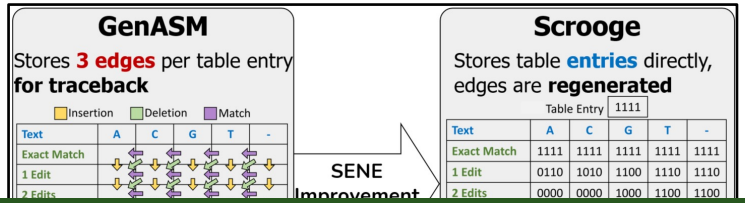
- |text|=|pattern|=k=64
- 12 thread blocks

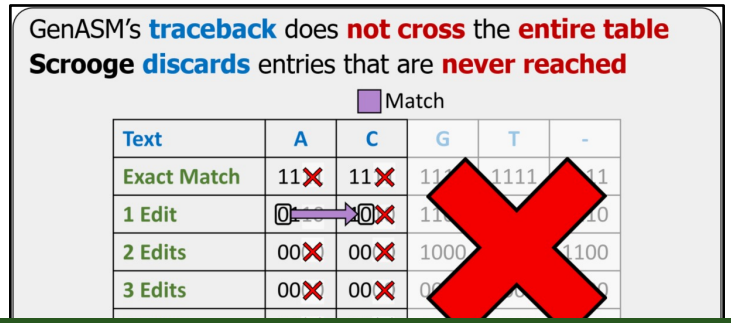
Footprint =64/2*64/2*1*64 bits * 12
=8KiB * 12
=96KiB

Shared memory capacity of he NVIDIA A6000 GPU: **99KiB** per SM

Implementation Attempt #4 – Scrooge

- **64 threads** in a thread block **cooperate** per seq. pair
- Store the DP table in **shared memory**
- **Algorithmically reduced memory footprint**





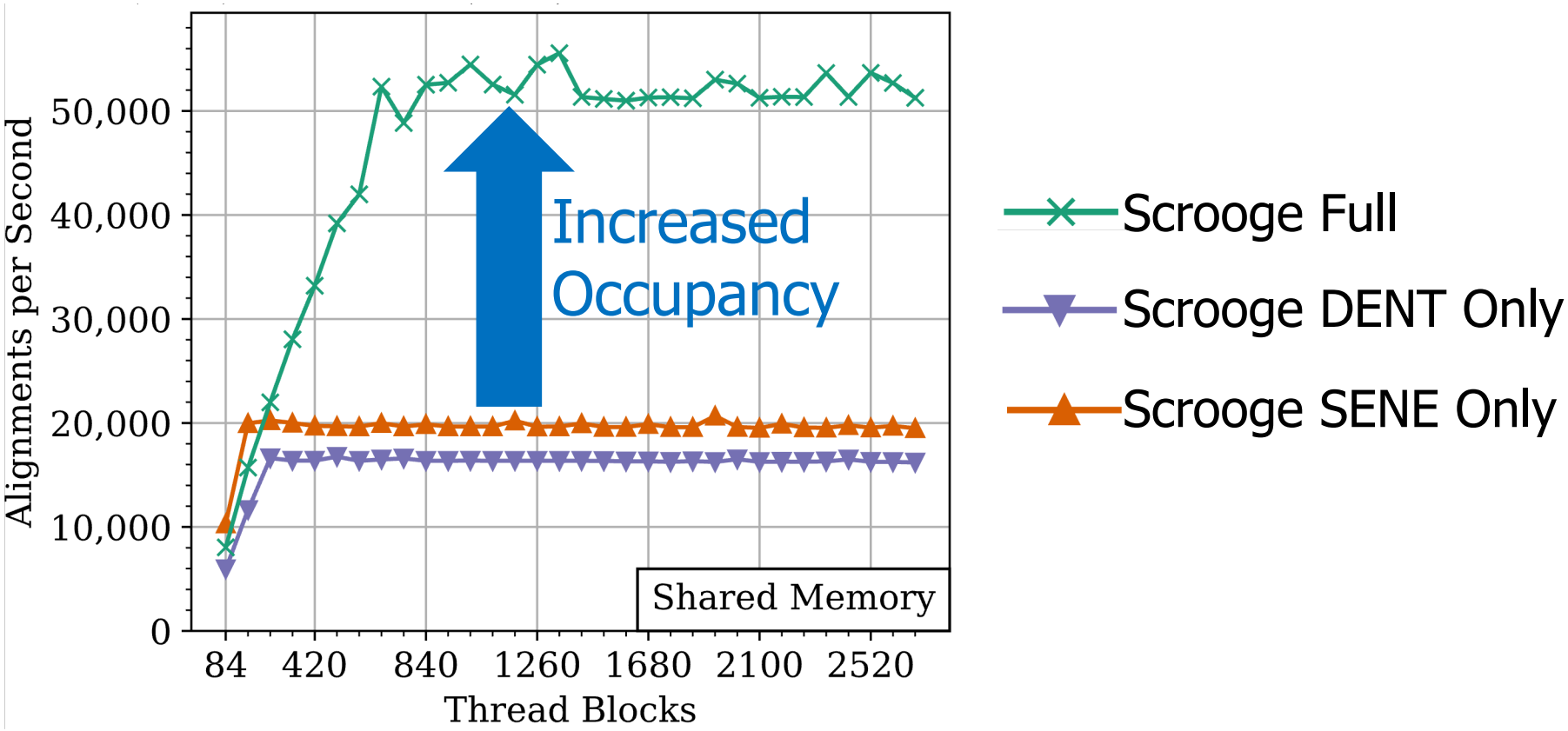
High performance

Thanks to high occupancy

SENE+DENT results in a **12x reduction** in **memory footprint** and **data movement**

Lindegger+, "Algorithmic Improvement and GPU Acceleration of the GenASM Algorithm", HiCOMB 2022

Scaling with Threadblocks



Generating Pattern Bitmasks

Pattern Bitmasks

- GenASM requires pre-computing ***"pattern bitmasks"***
  - **One-hot** (or one-cold) **encoding** of the **pattern** string

Pattern Bitmasks:

```
        CTGA
PM(A) = 1110
PM(C) = 0111
PM(G) = 1101
PM(T) = 1011
```

Pattern Bitmasks – Serial Implementation

Pattern Bitmasks:

```
        CTGA
PM(A) = 1110
PM(C) = 0111
PM(G) = 1101
PM(T) = 1011
```

```
__device__ PM_t generatePatternBitmask(int m, char *pattern){
 PM_t pm;
 pm[A] = ONES;
 pm[C] = ONES;
 pm[G] = ONES;
 pm[T] = ONES;
```

Initialize to all 1s

```
 for (int j = 0; j < m; j++){
```

For each char in pattern

```
  pm[pattern[j]] &= SINGLE_ZERO_AT(j);
 }
 return pm;
}
```

Set a 0

No parallelism

Only one thread per block does useful work

Pattern Bitmasks – Parallel Implementation

Pattern Bitmasks:

```
        CTGA
PM(A) = 1110
PM(C) = 0111
PM(G) = 1101
PM(T) = 1011
```

```
__device__ PM_t generatePatternBitmask(int m, char *pattern){
PM_t pm;
pm[A] = ONES;
pm[C] = ONES;
pm[G] = ONES;
pm[T] = ONES;
```

Initialize to all 1s

```
int j = threadIdx.x;
pm[pattern[j]] &= SINGLE_ZERO_AT(j);
```

Each thread sets a 0

```
for (int offset = 16; offset > 0; offset /= 2){
 //bitwise AND parallel reduction
 ...
}
```

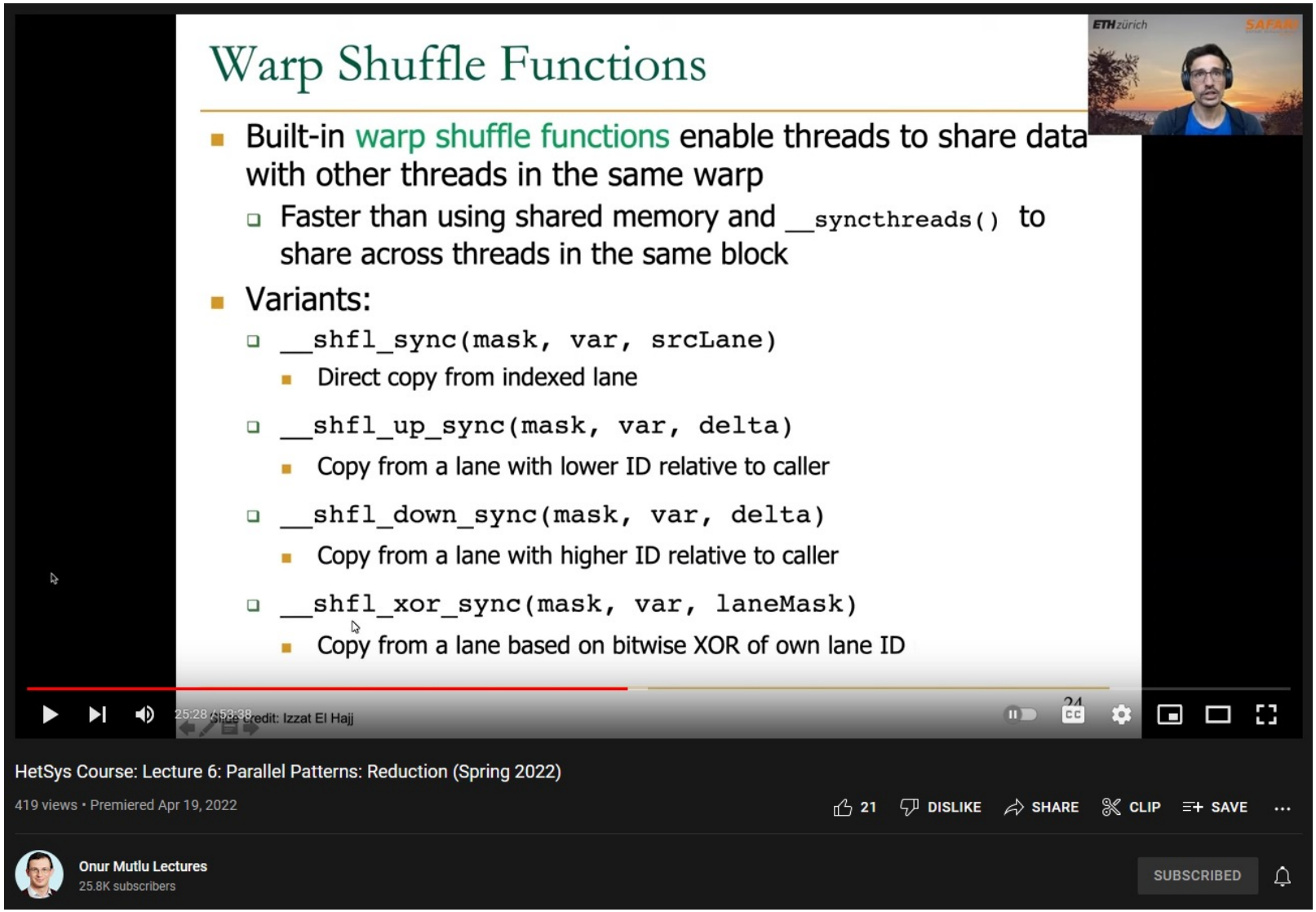
Merge results

```
return pm;
```

Large amount parallelism

Every thread in the block does useful work

More About Parallel Reductions



https://youtu.be/Xp0HHpcDwUc

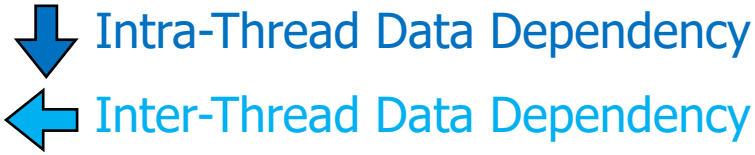
Resolving Data Dependencies

Recall: Mapping Threads to DP Cells

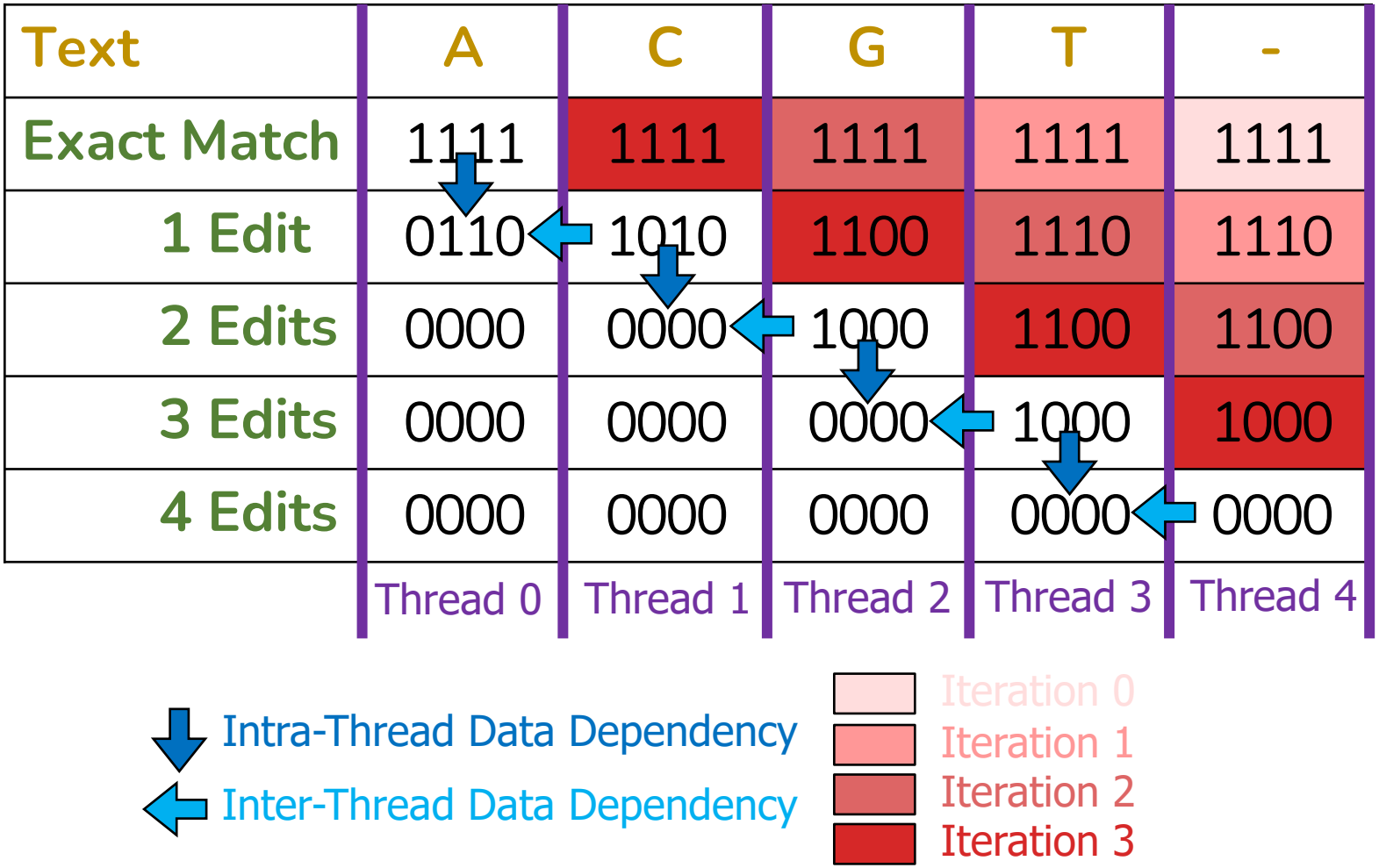
Text	A	C	G	T	-
Exact Match	1111	1111	1111	1111	1111
1 Edit	0110	1010	1100	1110	1110
2 Edits	0000	0000	1000	1100	1100
3 Edits	0000	0000	0000	1000	1000
4 Edits	0000	0000	0000	0000	0000
	Thread 0	Thread 1	Thread 2	Thread 3	

Data Dependencies

Text	A	C	G	T	-
Exact Match	1111	1111	1111	1111	1111
1 Edit	0110	1010	1100	1110	1110
2 Edits	0000	0000	1000	1100	1100
3 Edits	0000	0000	0000	1000	1000
4 Edits	0000	0000	0000	0000	0000
	Thread 0	Thread 1	Thread 2	Thread 3	Thread 4

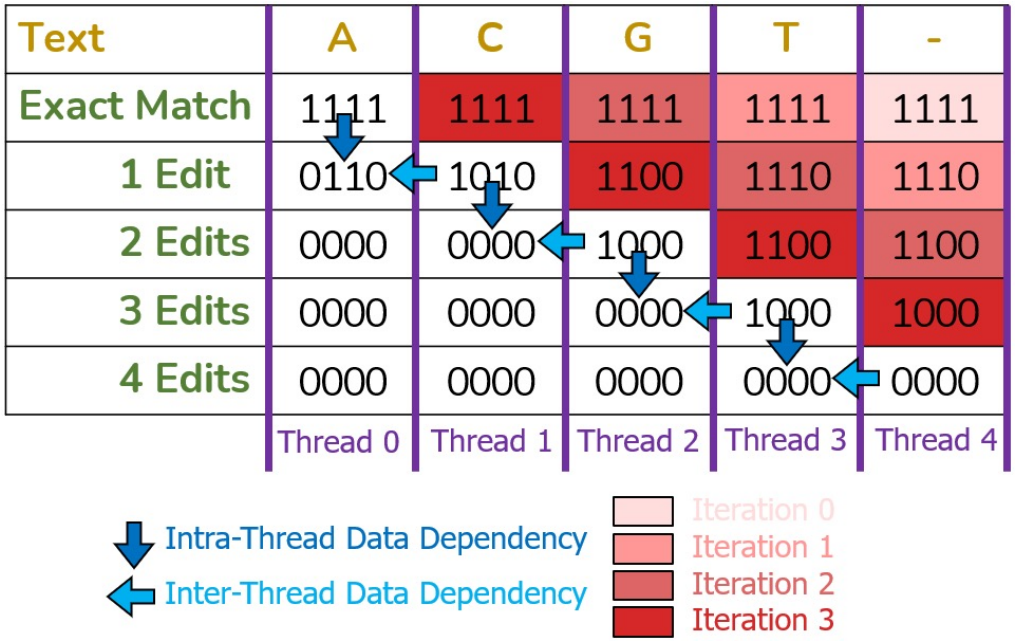


Data Dependencies



Resolving Data Dependencies

- **Memory accesses** can resolve all dependencies
  - But have undesirable **latency** and **bandwidth**
- **Register accesses** are preferred
  - Works **trivially** for vertical **intra-thread** dependencies
  - Does it also work for horizontal **inter-thread** dependencies?



Resolving Data Dependencies (cont'd)

- How to resolve **inter-thread** dependencies with registers?
  - Warp **shuffle** instructions!

B.22.1. Synopsis

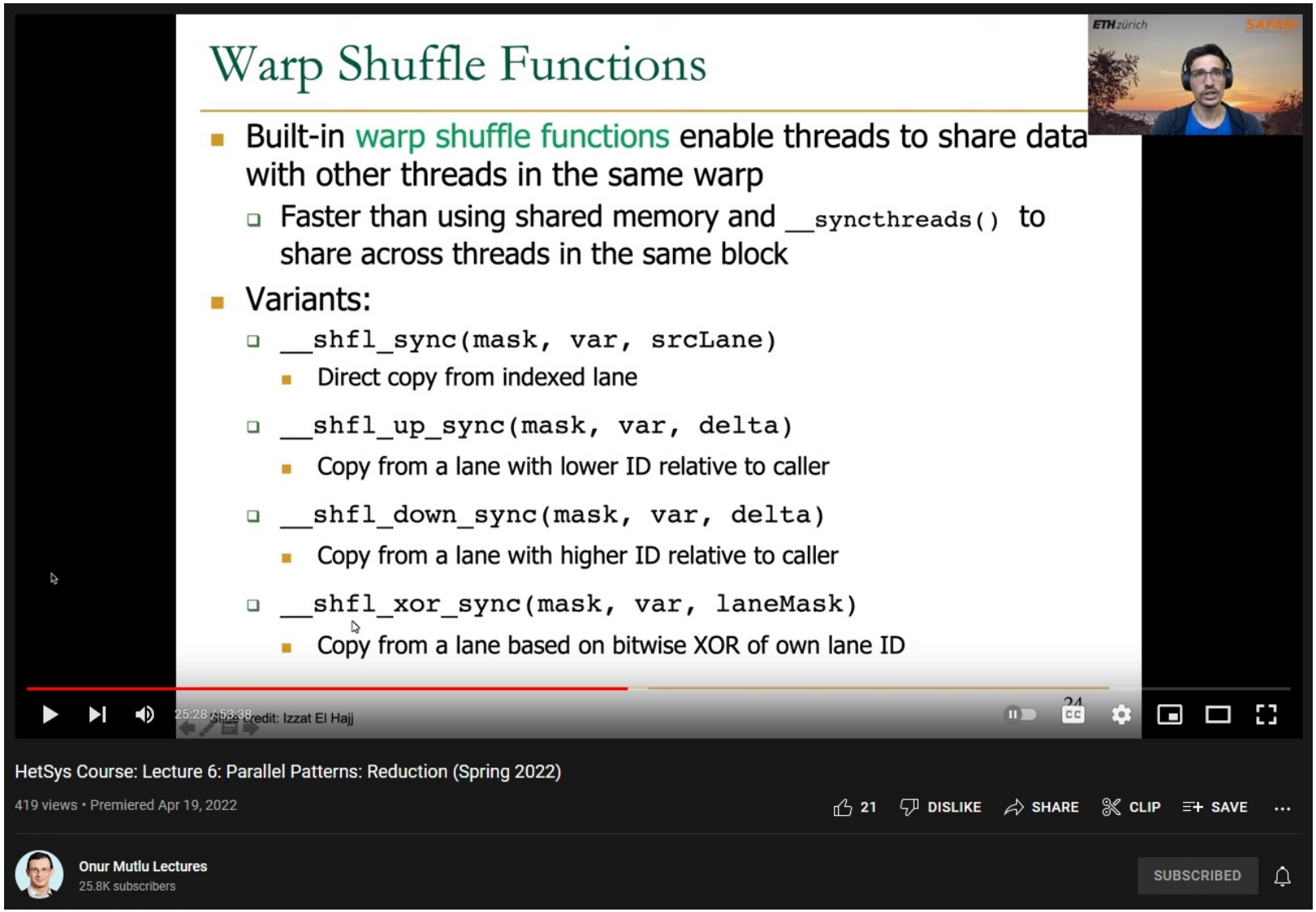
```
T __shfl_sync(unsigned mask, T var, int srcLane, int width=warpSize);
T __shfl_up_sync(unsigned mask, T var, unsigned int delta, int width=warpSize);
T __shfl_down_sync(unsigned mask, T var, unsigned int delta, int width=warpSize);
T __shfl_xor_sync(unsigned mask, T var, int laneMask, int width=warpSize);
```

B.22.2. Description

The `__shfl_sync()` intrinsics permit exchanging of a variable between threads within a warp without use of shared memory. The exchange occurs simultaneously for all active threads within the warp (and named in `mask`), moving 4 or 8 bytes of data per thread depending on the type.

https://docs.nvidia.com/cuda/cuda-c-programming-guide/index.html#warp-shuffle-functions

More About Warp Shuffle Functions



https://youtu.be/Xp0HHpcDwUc

Conclusion

Before:
1,800
alignments/second

- Shared Memory
- Thread Cooperative Implementation
- Algorithmic Improvements
- Bitmasks \w parallel reduction
- Data dependencies \w warp shuffle

After:
25,000
alignments/second

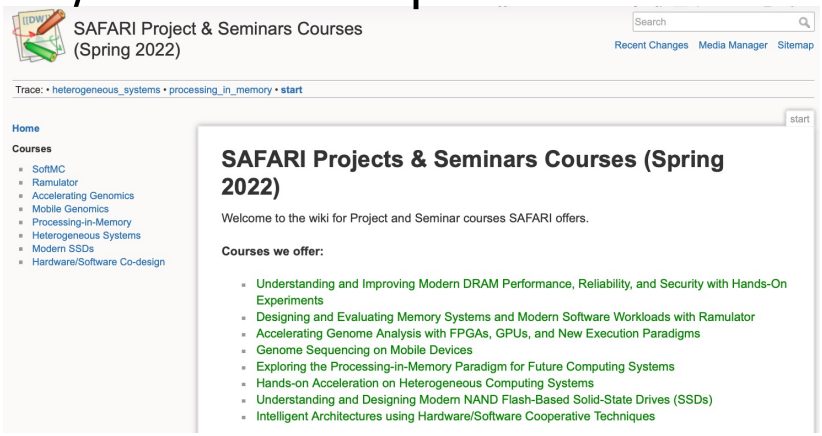
Optimizing GPU code requires a holistic view

Ignoring any of the above aspects would ruin the performance of the program

More P&S Courses: SSDs, Memory, Bioinformatics…

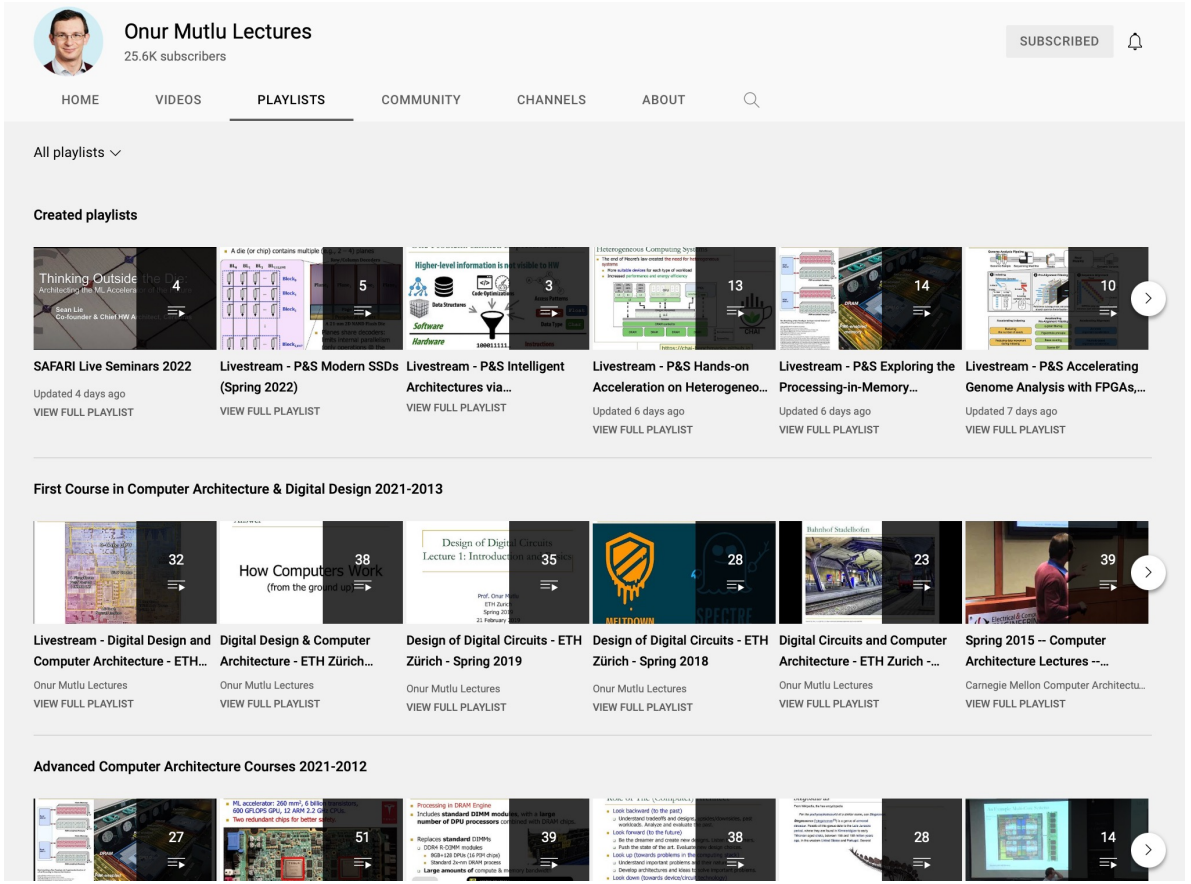
- Understanding and Improving Modern DRAM Performance, Reliability, and Security with Hands-On Experiments
- Designing and Evaluating Memory Systems and Modern Software Workloads with Ramulator
- Accelerating Genome Analysis with FPGAs, GPUs, and New Execution Paradigms
- Genome Sequencing on Mobile Devices
- Understanding and Designing Modern NAND Flash-Based Solid-State Drives (SSDs)
- Intelligent Architectures using Hardware/Software Cooperative Techniques

https://safari.ethz.ch/projects_and_seminars/spring2022/doku.php?id=start



More Resources: Onur Mutlu Lectures

- All P&S courses
- Digital Design and CompArch course
- Advanced CompArch course
- Seminar in CompArch



https://www.youtube.com/c/OnurMutluLectures/playlists

P&S Heterogeneous Systems

Algorithmic Improvement and GPU Acceleration of the GenASM Algorithm

Joël Lindegger
ETH Zürich

Fall 2022

23 January 2023